

that these alterations also contribute to diversity. Certain ginsenosides, such as Rb1 and Rg1, are poorly absorbed after ingestion (Odani *et al.*, 1983). Rb1 was hydrolyzed to compound K by intestinal flora (Karikura *et al.*, 1991); compound K was shown to increase the cytotoxicity of antineoplastic drugs (Hasegawa *et al.*, 1995) and to induce apoptosis in B16-BL6 melanoma cells (Wakabayashi *et al.*, 1998). Thus, it is also within the scope of the present invention that these altered ginsenosides may be modified or encapsulated to prevent alteration after oral administration. Prevention of structural alteration may result in enhancement of the ginsenoside.

It is also within the scope of the present invention to alter other physiologic effects or pharmacodynamics of the ginsenosides. These alterations include enhancement of the effects of the ginsenosides, *e.g.*, additive effects, synergism and potentiation. Thus, it is contemplated that there may be a synergistic effect and/or an additive effect between one or more than one ginsenoside or a ginsenoside(s) and another component(s) of the ginseng berry extract, *e.g.*, polysaccharides or fatty acids. One of skill in the art will realize that synergism may occur to produce an effect that is greater in magnitude to the sum of the effects when the compounds (*e.g.*, ginsenosides or other components of the ginseng berry) are given individually. Also, it will be realized that potentiation of compounds may occur. For example, but not limited to, a polysaccharide of the ginseng berry extract may not result in an anti-diabetic effect, however, in combination with a ginsenoside, the anti-diabetic effect may be enhanced beyond what is normal for the ginsenoside given alone.

II. Screening For the Active Compound of Ginseng Berry Extract

The present invention further comprises methods for identifying the active compound of ginseng berries. In specific embodiments, the ginseng berries are from the *Panax ginseng* (Asian ginseng) or *Panax quinquefolius* (American ginseng). These assays may comprise random screening of fruit extract for the candidate active compound or constituent. In particular, the assays may be used to focus on the particular ginsenoside moiety that is the active ginsenoside responsible for the anti-hyperglycemic effect and/or

the anti-obesity effect. It is also contemplated that the active compound may comprise non-ginsenoside constituents or be ginsenoside free or essentially ginsenoside free or a combination thereof.

These candidate active compound constituents are assayed for the ability to
5 modulate blood glucose, food intake, energy expenditure, plasma cholesterol, and/or body temperature.

To identify an active compound, one generally will prepare an extract of the fruit and analyze the extract. For example, a method generally comprises:

- (a) obtaining berry extract; and
- 10 (b) analyzing the extract for the active compound.

Analyzing may comprise separation of the extract into fractions. These fractions may be assayed further to determine a difference between the measured characteristics of the fractions. A difference in the characteristics of the fractions, such as the ability to decrease blood glucose levels, indicate that the candidate fraction is, indeed, a constituent
15 of the active compound.

Assays may be conducted in cell free systems, in isolated cells, or in organisms including transgenic animals.

It will, of course, be understood that all the screening methods of the present invention are useful in themselves notwithstanding the fact that effective candidates may
20 not be found. The invention provides methods for screening for such candidates, not solely methods of finding them.

A. Active Constituents

As used herein the term "candidate constituent or candidate substance" refers to any molecule that may potentially inhibit or enhance glucose utilization, body weight,

food intake, cholesterol level, or any other metabolic parameter. It is contemplated that the candidate constituent is a ginsenoside or derivative thereof. The present invention is not intended to be limited to ginsenosides, other possible candidate constituents include, but are not limited to saponins, polysaccharides, cholesterol, peptides, polyacetylenic
5 alcohols, fatty acids or other small molecules or derivatives thereof. It may prove to be the case that the most useful pharmacological compounds will be compounds that are structurally related to saponins. As used herein the term "saponin" refers to sapogenin glycosides, which is a type of glycoside widely distributed in plants. Saponins comprise a sapogenin, which constitutes the aglucon moiety of the molecule, and a sugar. It is
10 contemplated that the sapogenin may be a steroid or a triterpane and the sugar moiety may be glucose, galactose, a pentose, or a methylpentose. Using lead compounds to help develop improved compounds is known as "rational drug design" and includes not only comparisons with known inhibitors and activators, but predictions relating to the structure of target molecules.

15 The goal of rational drug design is to produce structural analogs of biologically active target compounds. By creating such analogs, it is possible to fashion drugs, which are more active or stable than the natural molecules, which have different susceptibility to alteration or which may affect the function of various other molecules. In one approach, one would generate a three-dimensional structure for a target molecule, or a fragment
20 thereof. This could be accomplished by x-ray crystallography, computer modeling or by a combination of both approaches.

It also is possible to use antibodies to ascertain the structure of a target compound. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass crystallography altogether by generating anti-idiotypic
25 antibodies to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of anti-idiotype would be expected to be an analog of the original antigen. The anti-idiotype could then be used to identify and isolate molecules from banks of chemically- or biologically-produced molecules.